Supplemental Table 1: Composition of diets

Product #	S8022-E127	S8022-E125	S8022-E126	S8022-E124
Ingredient (g)	**CON**	**MR**	**CON (+Cys)**	**MR (+Cys)**
L-Arginine	11.2	11.2	11.2	11.2
L-Lysine	18	18	18	18
L-Histidine	3.3	3.3	3.3	3.3
L-Leucine	11.1	11.1	11.1	11.1
L-Isoleucine	8.2	8.2	8.2	8.2
L-Valine	8.2	8.2	8.2	8.2
L-Threonine	8.2	8.2	8.2	8.2
L-Tryptophan	1.8	1.8	1.8	1.8
DL-Methionine	8.6	1.7	8.6	1.7
Glutamic acid	27	33.9	27	33.9
L-Phenylalanine	11.6	11.6	11.6	11.6
L-Tyrosine	4	4	4	4
Glycine	24.7	24.7	24.7	24.7
L-Cystine	-	-	3	3
L-Glutamine	11	11	11	11
L-Arspartic acid	6	6	6	6
L-Asparagine	6	6	6	6
L-Proline	6	6	6	6
L-Alanine	14	14	14	14
L-Serine	6	6	6	6
Corn Starch	264.0	264.0	264.0	264.0
Maltodextrin 10	170.0	170.0	170.0	170.0
Sucrose	110.0	110.0	107.0	107.0
Cellulose	50.0	50.0	50.0	50.0
Soybean Oil	25.0	25.0	25.0	25.0
Lard	133.5	133.5	133.5	133.5
Mineral Mix S10022G	35.0	35.0	35.0	35.0
Calcium Phosphate	2.5	2.5	2.5	2.5
Na Bicarbonate	2.0	2.0	2.0	2.0
Choline Bitrartrate	2.5	2.5	2.5	2.5
Vitamin Mix V10037	10.0	10.0	10.0	10.0
BHT	0.1	0.1	0.1	0.1
Food Dye	0.5	0.5	0.5	0.5
Sum (g)	1000	1000	1000	1000
kcal/gram	4.4	4.4	4.4	4.4
Protein (gm%)	18	18	18	18
Carbohydrate (gm%)	57	57	57	57
Fat (gm%)	16	16	16	16
Protein (kcal%)	16	16	16	16
Carbohydrate (kcal%)	52	52	52	52
Fat (kcal%)	32	32	32	32

Supplemental Table 2: Characteristics of the study population

	Omnivore (n=36)	**Vegan (n=36)**	**p-value**
Duration vegan diet [years]		4.8 (3.1-8.7)	
Men [%]	50% (18)	50% (18)	1.0
Age [years]	38.5 (32.0-46.0)	37.5 (32.5-44.0)	0.75
BMI [kg/m^2]	24.0 ± 2.1	22.9 ± 3.2	0.08
Physical Activity [h/week]	2.3 (1.2-4.1)	2.8 (0.88-3.75)	0.69
Smoking status (%)			0.30
Non-smoker	58.3% (21)	66.7% (24)	
Ex-Smoker	16.7% (6)	22.2% (8)	
Smoker	25.0% (9)	11.1% (4)	
Plasma methionine			
Methionine [µM]	26.8 (25.9-29.9) Min=22.1; Max=39.4	26.7 (24.3-30.4) Min=19.6; Max=38.5	0.32
Plasma leptin/adiponectin ratio			
leptin/adiponectin ratio	1.14 (0.53-2.14) Min=0.10; Max=6.53	0.90 (0.51-1.32) Min=0.01; Max=4.69	0.30

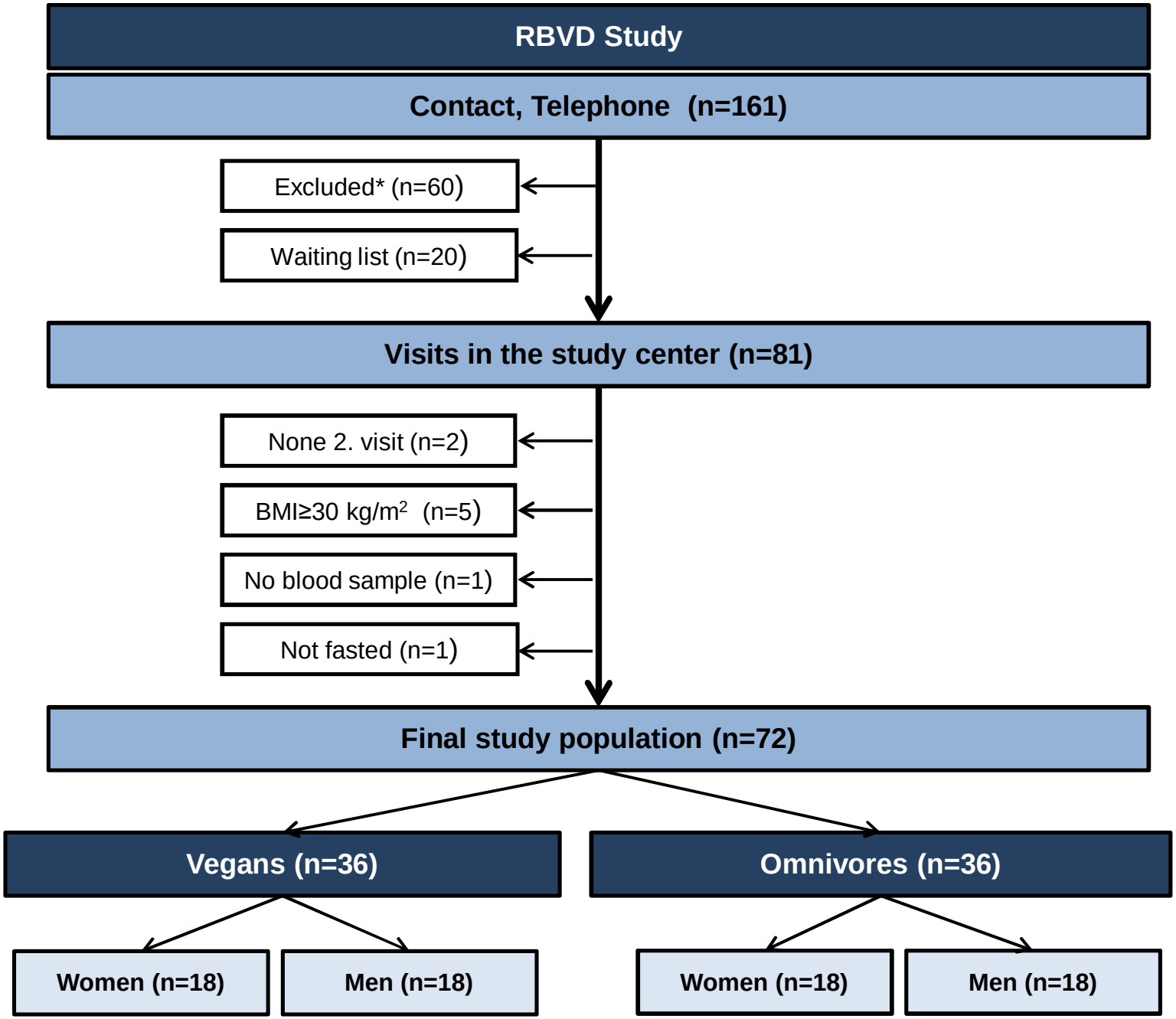
Variables expressed as percentage or mean ± SD or median (IQR)

Supplemental Table 3: Antibodies and ELISA

Antibody	Product #	Company	Dilution
Adiponectin	Ab3455	Abcam	1:500
α-Tubulin	T 6074	Sigma	1:500
protein kinase B (PKB/Akt)	9272	Cell Signaling	1:1,000
phospho-Akt Ser^{473}	9271	Cell Signaling	1:1,000
PEPCK	LS-C401843/121776	LSBio	1:600
GAPDH	AM4300	ThermoFisher	1:25,000
HRP-conjugated anti-mouse IgG	315-035-008	Dianova	1:20,000
HRP-conjugated anti-rabbit IgG	111-035-008	Dianova	1:20,000
DyLightTM 680 conjugated anti-mouse IgG	35519	Thermo Scientific	1:15,000
DyLightTM800 4X-PEG anti-rabbit	SA5-35571	Thermo Scientific	1:15,000

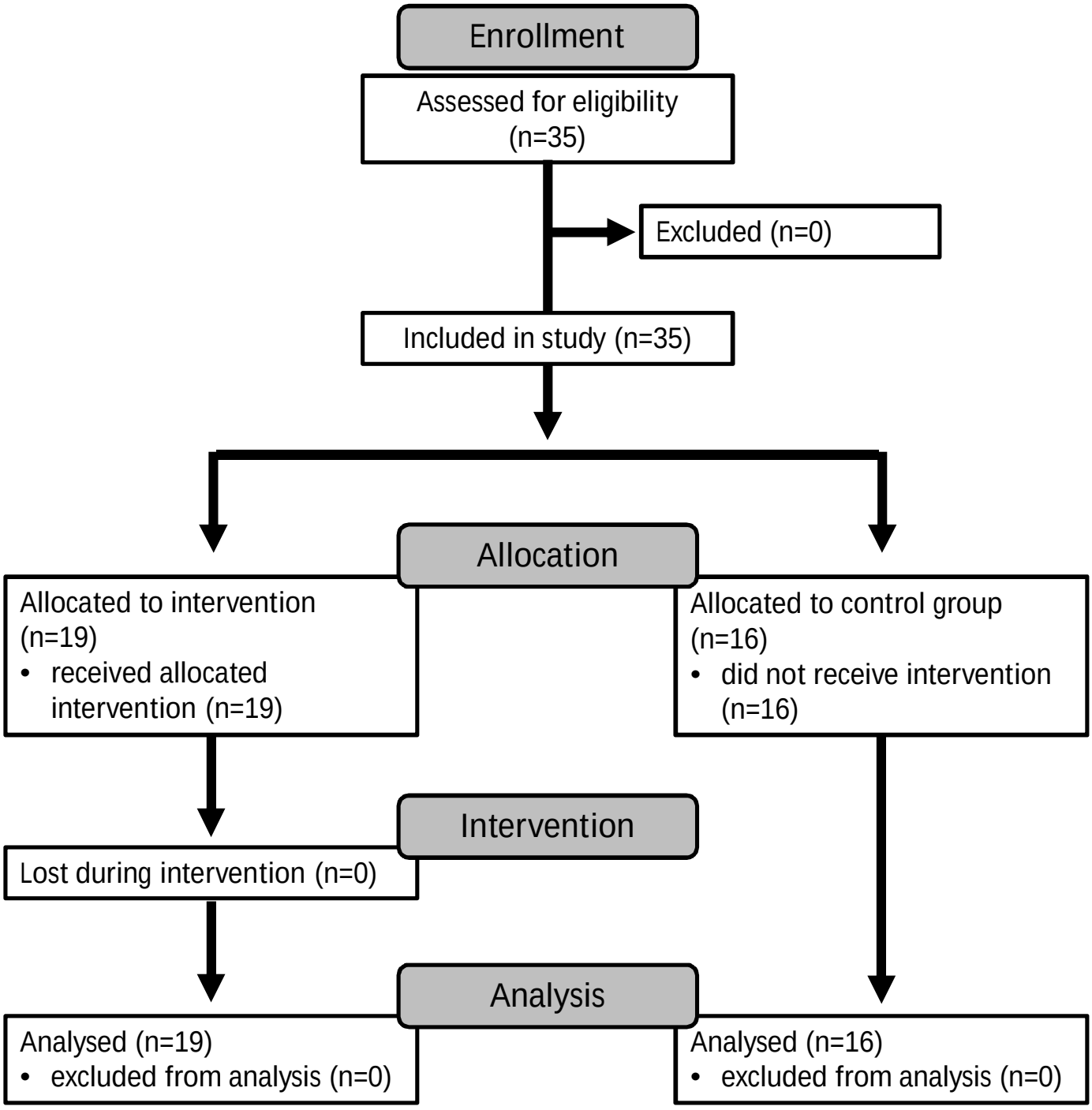
ELISA

Adiponectin (Mouse) Total, HMW ELISA	47-ADPMS-E01	ALPCO
Adiponectin (Acrp30) (Human Total) ELISA	80-ADPHUT-E01-AL	ALPCO
Human FGF-21 ELISA	RD191108200R	BioVendor
Human Leptin Quantikine ELISA Kit	DLP00	R&D Systems
Human Total Adiponectin/Acrp30 Quantikine ELISA Kit	DRP300	R&D Systems
Insulin	80-INSMSU-E01	ALPCO
Leptin Human ELISA, Clinical Range	RD191001100	BioVendor
Mouse and Rat FGF-21 ELISA	RD291108200R	BioVendor
Mouse/Rat Leptin Quantikine ELISA Kit	MOB00	R&D Systems

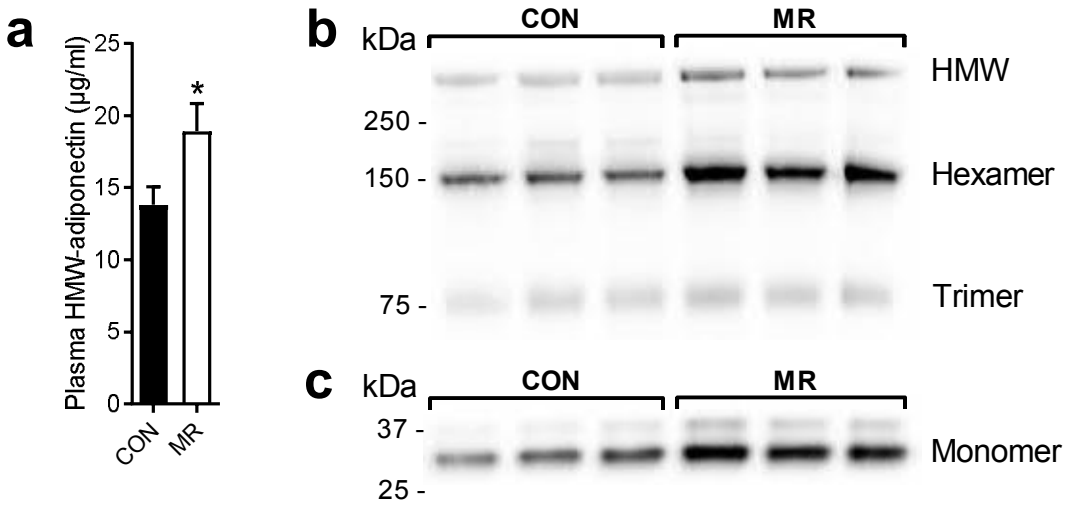


*Due to: high expenditure of time, vegan nutrition, but >1 exception in 3 month, flexitarians, vegetarians, to young, overweigth, prevalent cancer, pregnant, breastfeeding, declined stool or urine sampling

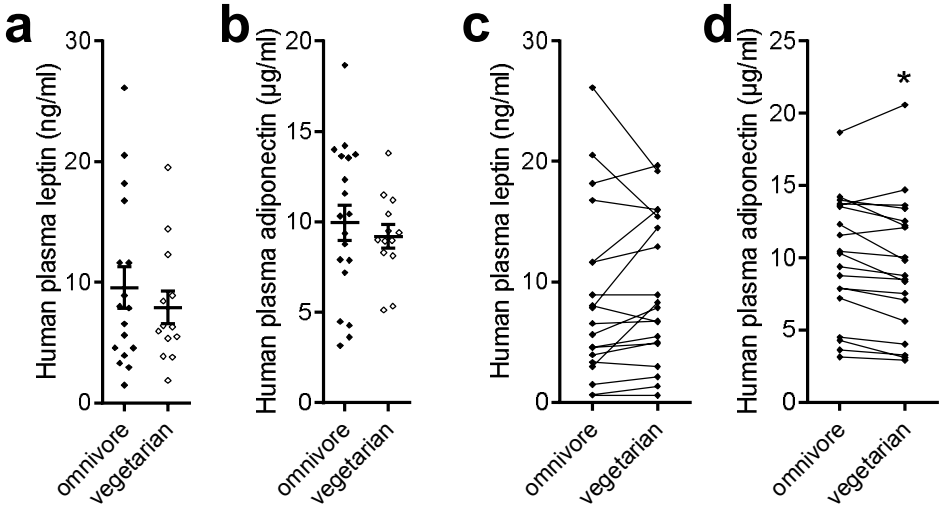
Supplemental Figure 1. Flow chart of the study participants.



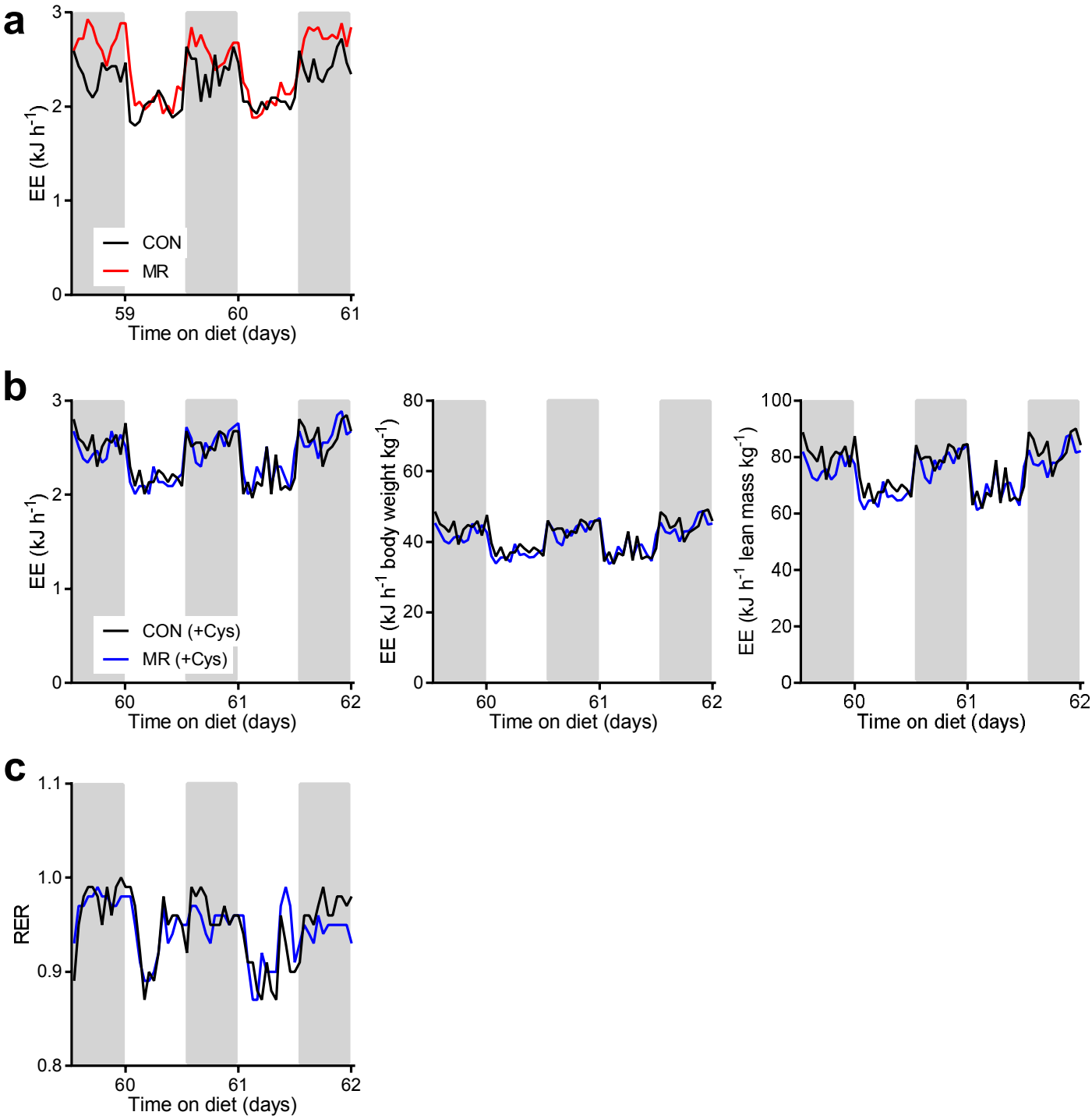
Supplemental Figure 2. Flow chart of the study participants.



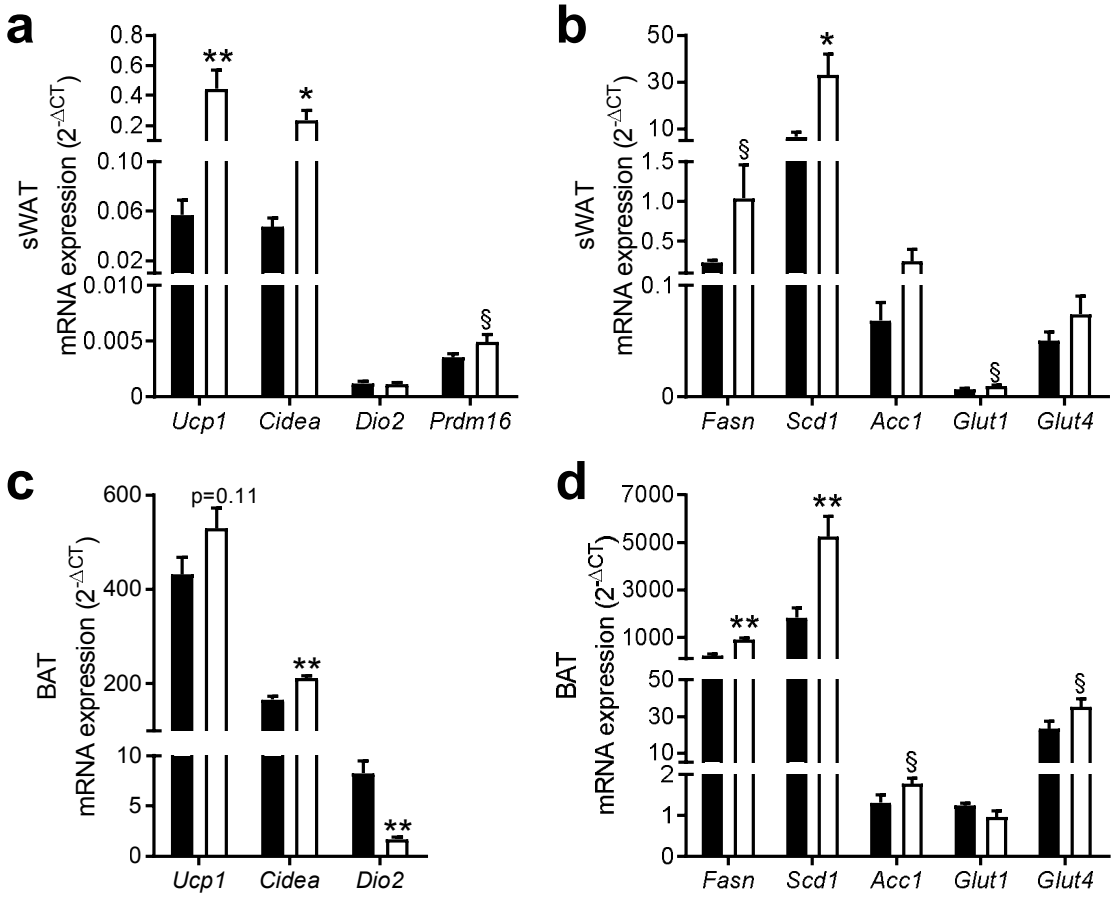
Supplemental Figure 3. Methionine restriction induces high molecular weight adiponectin. Plasma was collected from mice that were treated as described in Fig. 1. Nine weeks after the diet switch, 6h fasted mice were killed. (**a**) Final circulating high molecular weight (HMW) adiponectin levels assessed by ELISA. (**b, c**) Final plasma adiponectin isoforms assessed by western blot. Data are presented as means ± SEM (n = 6/group). Differences vs the CON group were calculated by using a two-tailed *t* test (**a**). *$p \leq 0.05$.



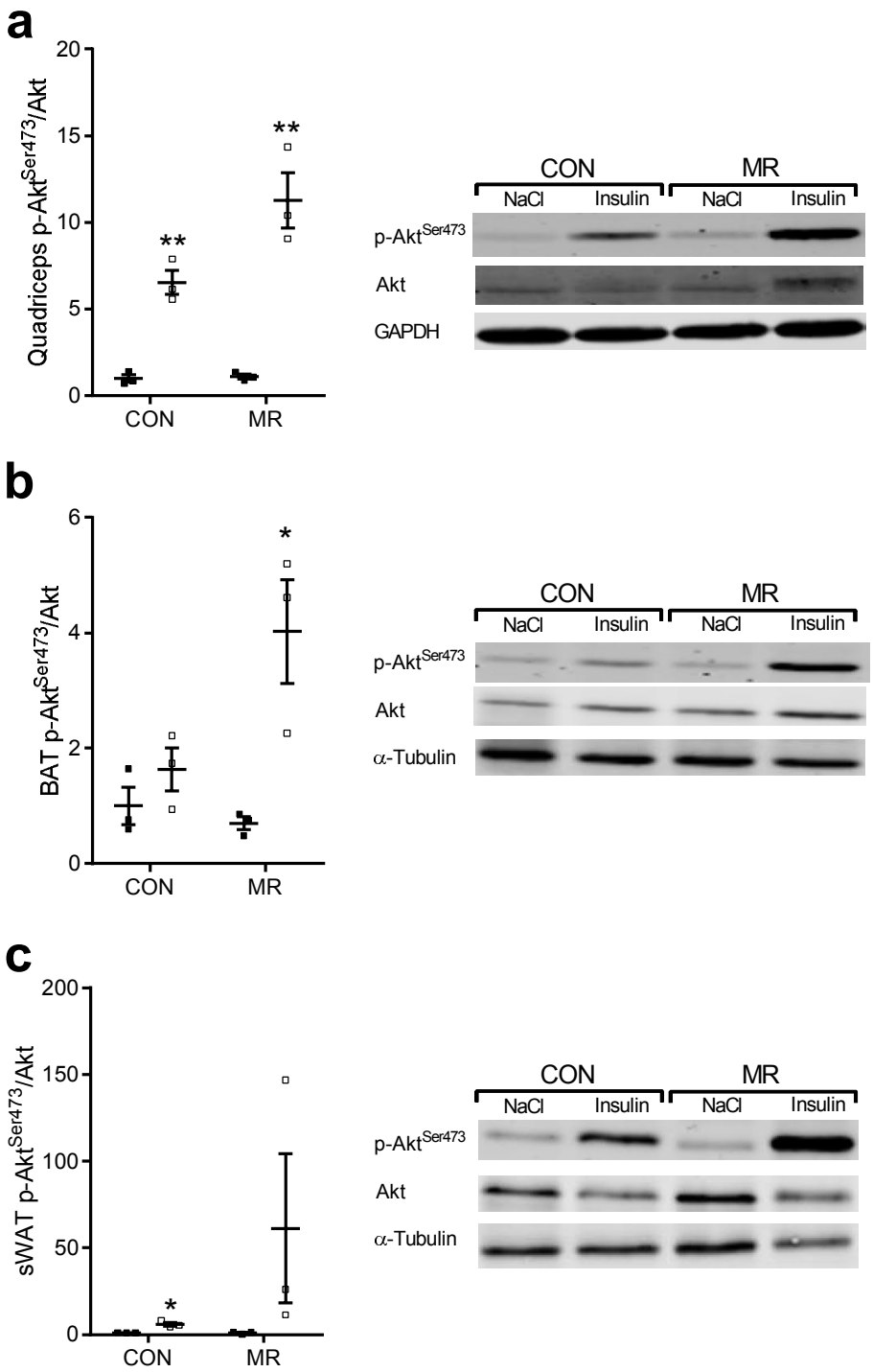
Supplemental Figure 4. Effects of a vegetarian diet on circulating adipokines in humans. (**a**) Plasma leptin and (**b**) adiponectin concentrations of omnivore (n=19) or ovo-lacto vegetarian (n=13) humans at baseline. (**c**) Plasma leptin and (**d**) adiponectin concentrations of omnivore human subjects (n=19) given an ovo-lacto vegetarian diet for 4 days. Data are presented as means ± SEM. Differences between groups were calculated by using a two-tailed *t* test (**a-b**) and paired two-tailed *t* test (**c-d**). *$p \leq 0.05$.



Supplemental Figure 5. Effects of methionine restriction on energy expenditure. Mice were treated as described in Fig. 1. (**a**) Energy expenditure (EE) in NZO mice consuming CON or MR diets for 8 weeks. (**b**) EE in NZO mice consuming CON (+Cys) or MR (+Cys) diets for 8 weeks. EE normalised to body weight or lean mass. (**c**) Respiratory exchange ratio (RER) in NZO mice consuming CON (+Cys) or MR (+Cys) diets for 8 weeks. Data are presented as means (n = 4-6/group).



Supplemental Figure 6. Effects of methionine restriction on gene expression in fat depots. Tissues were collected from mice that were treated as described in Fig. 1. Nine weeks after the diet switch, 6h fasted mice were killed. Thermogenetic genes from (**a**) sWAT and (**c**) BAT, and lipogenic and glucose transporter genes from (**b**) sWAT and (**d**) BAT were measured via real-time PCR. Target gene expression in sWAT and BAT was normalised to beta-actin (*Actb*) and TATA box binding protein (*Tpb*), respectively. Black bars, CON; white bars, MR. Data are presented as means $\pm$ SEM (n = 6/group). Differences between groups were calculated by using a two-tailed *t* test (**a-d**). $^{\S}0.1>p>0.05$; *$p \leq 0.05$; **$p \leq 0.01$.



Supplemental Figure 7. Effects of dietary methionine restriction on insulin sensitivity in NZO mice. Mice were treated as described in Fig. 1. Nine weeks after the diet switch, mice fasted for 6 h were treated intraperitoneally with NaCl or insulin (7 IU/BWkg) 15 min before killing. Western blots of total and phosphorylated Akt in (**a**) quadriceps, (**b**) brown adipose tissue, and (**c**) subcutaneous white adipose tissue. Detecting GAPDH (glyceraldehyde 3-phosphate dehydrogenase) or α-Tubulin was used as loading control. Black squares, NaCl; white squares, insulin. Data are presented as means $\pm$ SEM (n = 3/group). Differences between the groups were calculated by using a two-tailed *t* test (**a-c**). *$p \leq 0.05$; **$p \leq 0.01$.